Title

Cross-Sectional and Longitudinal Associations of Chronic Posttraumatic Stress Disorder With Inflammatory and Endothelial Function Markers in Women

Journal

Biological Psychiatry, 82(12)

ISSN

0006-3223

Authors

Sumner, Jennifer A
Chen, Qixuan
Roberts, Andrea L
et al.

Publication Date

2017-12-01

DOI

10.1016/j.biopsych.2017.06.020

Peer reviewed

HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2018 December 15.

Published in final edited form as:

Biol Psychiatry. 2017 December 15; 82(12): 875–884. doi:10.1016/j.biopsych.2017.06.020.

Cross-Sectional and Longitudinal Associations of Chronic Posttraumatic Stress Disorder with Inflammatory and Endothelial Function Markers in Women

Jennifer A. Sumner[a,b,*], **Qixuan Chen**[c], **Andrea L. Roberts**[d], **Ashley Winning**[d], **Eric B. Rimm**[b,e,f], **Paola Gilsanz**[d], **M. Maria Glymour**[g], **Shelley S. Tworoger**[b,f], **Karestan C. Koenen**[b,h], and **Laura D. Kubzansky**[e]

[a]Center for Behavioral Cardiovascular Health, Columbia University Medical Center, New York, NY

[b]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[c]Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY

[d]Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA

[e]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[f]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[g]Department of Epidemiology and Biostatistics, University of California San Francisco School of Medicine, San Francisco, CA

[h]Psychiatric and Neurodevelopmental Genetics Unit and Department of Psychiatry, Massachusetts General Hospital, Boston, MA

Abstract

Background—Posttraumatic stress disorder (PTSD) may contribute to heightened cardiovascular disease (CVD) risk by promoting a pro-inflammatory state and impaired endothelial function. Prior research has demonstrated associations of PTSD with inflammatory and endothelial function biomarkers, but most work is cross-sectional and does not separate effects of trauma exposure from those of PTSD.

Methods—We investigated associations of trauma exposure and chronic PTSD with biomarkers of inflammation [C-reactive protein (CRP); tumor necrosis factor-alpha receptor-II (TNFRII)] and endothelial function [intercellular adhesion molecule-1 (ICAM-1); vascular cell adhesion

[*]Correspondence to: Jennifer Sumner, Center for Behavioral Cardiovascular Health, Columbia University Medical Center, 622 W. 168th St, PH 9-315, New York, NY 10032. Tel: 212-342-3133; Fax: 212-342-3431; js4456@cumc.columbia.edu.

Financial Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

molecule-1 (VCAM-1)] in 524 middle-aged women in the Nurses' Health Study II. Using linear mixed models, we examined associations of trauma/PTSD status with biomarkers measured twice, 10–16 years apart, in CVD-free women, considering either average levels over time (cross-sectional) or change in levels over time (longitudinal). Biomarker levels were log-transformed. Trauma/PTSD status (based on structured diagnostic interviews) was defined as no trauma at either blood draw (n=175), trauma at draw 1 but no PTSD at either draw (n=175), and PTSD that persisted beyond draw 1 (chronic PTSD; n=174). The reference group was women without trauma.

Results—In models adjusted for known potential confounders, women with chronic PTSD had higher average CRP (b=0.27, p<.05), TNFRII (b=0.07, p<.01), and ICAM-1 (b=0.04, p<.05) levels. Women with trauma but without PTSD had higher average TNFRII levels (b=0.05, p<.05). Furthermore, women with chronic PTSD had a greater increase in VCAM-1 over time (b=0.003, p<.05).

Conclusions—Increased inflammation and impaired endothelial function may be pathways by which chronic PTSD increases CVD risk.

Keywords

Trauma; posttraumatic stress disorder; inflammation; endothelial cell adhesion molecules; women; biomarkers

Introduction

Numerous studies have linked trauma and posttraumatic stress disorder (PTSD) to increased risk of cardiovascular disease (CVD)(1–5). PTSD is characterized by neurobiological alterations that may contribute to CVD, including dysregulation of the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary system(6,7). Additionally, trauma exposure—even in the absence of psychopathology—is associated with dysfunctional biological stress responses, although alterations are generally smaller than those associated with PTSD(8,9). These physiological changes contribute to adverse downstream effects on health-relevant biological processes, including increased systemic inflammation and impaired endothelial function(7,10). Inflammatory and endothelial responses both contribute to atherosclerosis(11,12) and are influenced by stress-related elevations in corticosteroids and catecholamines(13). These processes interact in a complex cascade of events, and are thought to reflect underlying vascular inflammation(13,14).

Two recent meta-analyses provide compelling cross-sectional evidence linking trauma exposure and PTSD with higher inflammation. In one, Tursich et al.(15) demonstrated trauma exposure was moderately correlated with elevated pro-inflammatory cytokine levels, as measured by interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α), and acute-phase protein levels, as measured by C-reactive protein (CRP). However, contributions of trauma versus trauma-related psychopathology could not be considered because too few studies had relevant data(15). In the other, Passos et al.(16) investigated the association of PTSD (rather than trauma per se) with inflammation. Compared to healthy controls, individuals with PTSD had higher levels of IL-1β, IL-6, interferon γ, and—in patients without medication—TNF-α, with medium to large effect sizes. Notably, associations

between PTSD and elevated TNF-α, IL-1β, and IL-6 remained significant when excluding participants with comorbid depression, another form of psychopathology also associated with a pro-inflammatory state(17,18). Fewer studies have investigated associations of trauma and PTSD with endothelial function biomarkers. Although some evidence suggests that PTSD is associated with elevated levels of endothelial cell adhesion molecules that play an early role in the accumulation of lipids within the arterial wall(14), including intercellular adhesion molecule-1 (ICAM-1)(19–21) and vascular cell adhesion molecule-1 (VCAM-1) (20), findings have been inconsistent(19,22).

Existing literature linking trauma and PTSD with cardiovascular biomarkers has two key limitations. First, most studies have conflated trauma exposure and PTSD (although see(21,23) for exceptions). Thus, it is unclear whether trauma or psychological response to trauma is the relevant exposure with respect to increased inflammation and impaired endothelial function. Second, most studies have been cross-sectional. One small study (*N*=55) assessed biomarker change from when PTSD was assessed to 2.5 years later and found inflammatory and endothelial marker increases associated with elevated PTSD symptoms(21). In contrast, an all-male study (*N*=101) comparing biomarker levels measured twice, 3 months apart, in combat veterans with PTSD and healthy controls found no differences(24). With so few studies with longitudinal data, whether trauma and/or PTSD are associated with changes in biomarker levels over time is still unclear.

To address these knowledge gaps, we examined cross-sectional and longitudinal associations of trauma exposure and chronic PTSD with level and change in CRP, TNF-α receptor-II (TNFRII), ICAM-1, and VCAM-1 in 524 middle-aged women in the Nurses' Health Study II (NHS II). Biomarkers were measured twice, 10–16 years apart. The specific biomarkers were selected based on their relevance to CVD risk, their potential to be altered in response to activation of stress-related biological processes that have been linked to PTSD (see(13) for a review), and because they can be reliably assayed in plasma. Prior work has laid out biological processes linking stress to high levels of inflammation and ultimately CVD via elevations in corticosteroids and catecholamines that promote elevations in blood pressure and blood flow(13). These changes modify acute phase proteins and adhesion molecule activity, leading to endothelial damage, inflammation, and ultimately initiation of disease processes. CRP, TNFRII, and ICAM-1 have predicted risk of incident CVD events in women(25,26), and all the biomarkers selected have been linked to increased cardiometabolic disease risk within the larger NHS sample(26,27).

We hypothesized biomarker levels would be higher and increase more over time among women with chronic PTSD versus no trauma. Additionally, we predicted women with trauma but no PTSD would have higher biomarker levels and greater increases compared to those with no trauma, although not as substantial as women with chronic PTSD. Drawing on prior literature, we identified relevant covariates for consideration, including several factors (e.g., weight status, cigarette smoking) that might lie on the pathway between PTSD and dysregulated inflammatory processes or endothelial function(15,16).

Methods and Materials

Participants and Procedure

Women were participants in the NHS II, a longitudinal study of 116,429 female U.S. nurses enrolled in 1989 at ages 25–42 years and followed biennially. Blood samples were collected in 1996–1999 (draw 1) when women were 32–52 years of age and again in 2008–2012 (draw 2) when women were 46–65 years of age(28). The current study included 524 women who completed the PTSD substudy, had a blood sample from both draws, and had no history of CVD (see Supplemental Methods)(29,30). This study was approved by the Partners Healthcare Human Research Committee; return of questionnaires by mail represented implied consent.

Trauma and PTSD Assessment

Women in the PTSD substudy completed a supplemental trauma exposure and PTSD screening questionnaire in 2008(31,32). Lifetime trauma exposure was assessed with a modified version of the Brief Trauma Questionnaire(33). Women reported which event was their worst experience and if they ever experienced any of seven PTSD symptoms in relation to their worst trauma on the Short Screening Scale for *DSM-IV* PTSD(34). A subset of women who reported trauma exposure on the screening questionnaire also completed diagnostic interviews to determine PTSD case status (n=3,013).

Criteria for selection into trauma/PTSD status groups were stringent. From those eligible, we randomly selected three groups of 175 women each: 1) a no trauma group comprising women who reported no lifetime trauma exposure on the 2008 screening questionnaire nor any childhood moderate or severe sexual abuse or serious physical-emotional abuse on a 2001 questionnaire querying violence exposure(35) (175 women out of 1,174 eligible; women who were and were not selected for the no trauma reference group were highly similar on all covariates included in our models); 2) a trauma/no PTSD group who reported exposure to their worst trauma prior to the first blood draw but few (if any) symptoms of PTSD in response to that trauma on the interview (i.e., PTSD total severity score of 17–19 out of a possible range of 17–85; 175 out of 187 eligible); and 3) a chronic PTSD group comprising women whose worst trauma occurred prior to the first blood draw and led to PTSD that persisted beyond the first draw (175 out of 220 eligible; see Supplemental Methods).

Biomarker Assays

Assays to determine plasma biomarker concentrations were conducted by the Clinical and Epidemiologic Research Lab at Children’s Hospital Boston. High-sensitivity CRP was measured using an immunoturbidimetric assay on the Roche P Modular system (Roche Diagnostics-Indianapolis, IN), using reagents and calibrators from DiaSorin (Stillwater, MN). TNFRII, ICAM-1, and VCAM-1 concentrations were quantified using ELISA assays (R&D Systems, Minneapolis, MN). Two assays per individual were available for each biomarker, one from each blood draw, but assays for both draws were conducted at the same time. Assays were conducted in two sets. Mean intra-assay coefficients of variability (CVs; indicating within-plate precision) for the two sets were 3.4% and 3.3% for CRP, 6.1% and

4.4% for TNFRII, 3.6% and 2.3% for ICAM-1, and 5.7% and 3.1% for VCAM-1. Mean inter-assay CVs (indicating plate-to-plate consistency) for the two sets were 3.1% and 2.9% for CRP, 4.6% and 4.3% for TNFRII, 2.3% and 1.9% for ICAM-1, and 3.7% and 3.2% for VCAM-1.

Covariates

We considered a range of covariates, including potential confounders such as age at the first blood draw, race (White, non-White, missing), anti-hypertensive medication use, anti-inflammatory medication use, cholesterol-lowering medication use, menopausal status (pre-menopausal, post-menopausal, unknown status), and past-month hormone therapy use (yes, no, not applicable/missing). Age and race were assessed at draw 1 and the NHS II baseline, respectively. All other variables were time-updated to reflect their status at each draw. Most variables were assessed with self-report from the questionnaire administered at each blood draw, except anti-inflammatory, anti-hypertensive, and cholesterol-lowering medication use, which were measured at the closest preceding biennial questionnaire.

We also examined several health behaviors and body mass index (BMI), given these might be on the pathway linking trauma/PTSD status with inflammation and impaired endothelial function. Self-reported behaviors and BMI were available either from the blood draw questionnaires or closest biennial questionnaire. BMI in kg/m^2 was calculated from self-reported height and weight (validated in prior NHS II research(36)). Women also reported their past-month cigarette smoking (0 cigarettes/day, 1–4/day, 5+/day), alcohol consumption (0 drinks, 1–3/month, 1/week, 2–4/week, 5+/week), and physical activity (<1 time/week, 1/week, 2–3/week, 4+/week). Diet quality was quantified based on the Alternate Healthy Eating Index(37); scores range from 0–110 (higher scores indicate a healthier diet).

In a sensitivity analysis, we considered depression status and antidepressant use as potential confounders. Depression status at draw 1 was derived from responses to the 5-item Short Form-36 Mental Health scale(38) administered in 1997; following prior work with this measure, depression was defined as a score <53(39). Depression status at draw 2 was defined as a history of clinician diagnosis of depression reported on biennial questionnaires administered between draws 1 and 2 or reported major depression on a modified version of the Patient Health Questionnaire (PHQ-9)(40) administered with the PTSD interview and scored based on *DSM-IV* criteria. Antidepressant use was assessed on each blood draw questionnaire.

Analytic Approach

We first compared the distribution of covariates across trauma/PTSD groups (no trauma, trauma/no PTSD, chronic PTSD) at draw 1 using chi-squared tests, Fisher's exact tests, and analyses of variance. Next, we evaluated inflammatory marker and endothelial cell adhesion molecule levels at each draw for each trauma/PTSD group, and calculated change in biomarker levels over the 10–16 years between draws. Due to skew in biomarker data, we calculated medians and interquartile ranges. For subsequent analyses, biomarker concentrations were log-transformed to normalize their distributions (see Figures S1–S4 for

histograms and boxplots of distributions of raw and log-transformed biomarker values and Supplemental Methods for biomarker data processing details).

To examine cross-sectional and longitudinal associations of trauma/PTSD status with inflammatory marker and endothelial cell adhesion molecule levels, we fit a series of linear mixed models for each biomarker(41) (see Supplemental Methods for detailed description of analyses). To assess cross-sectional associations, trauma/PTSD status was coded categorically (no trauma was the reference group); these terms estimated differences in average biomarker levels across the two draws for each trauma/PTSD group relative to the no trauma group. To assess longitudinal associations, trauma/PTSD status × time interaction terms evaluated whether change rates in biomarker values over time varied by trauma/PTSD group. To contextualize the log-transformed biomarker linear mixed model findings in terms of raw biomarker values, we computed least-squares geometric means and 95% confidence intervals (CIs) of biomarker values(28). Models were first adjusted for time in years between draws and age at draw 1 and then further adjusted for race and time-updated measures of covariates (medication use and menopausal status). We also examined how adding time-updated measures of potential pathway variables—grand-mean centered BMI, cigarette smoking, alcohol consumption, physical activity, and grand-mean centered diet quality—influenced associations of trauma/PTSD status with biomarker levels.

To investigate the potential influence of outliers, we re-fit the trauma/PTSD main effect and trauma/PTSD × time interaction models based on a 90 percent Winsorization, whereby the bottom 5% of each raw biomarker value was set to the value corresponding to the 5^{th} percentile and the upper 5% of raw values were set to the value corresponding to the 95^{th} percentile. Log-transformed Winsorized biomarker values were the outcomes in these models. We also conducted two sensitivity analyses. We considered potential confounding by depression by adding time-updated depression status and antidepressant use to time- and age-adjusted models. Additionally, we examined if time between trauma and blood draw was associated with biomarker levels for women in the trauma/no PTSD and chronic PTSD groups.

Results

Descriptive Statistics

The analytic sample comprised 524 women; 1 woman in the chronic PTSD group did not have analyzable biomarker data, resulting in 174 women in that group. Participant characteristics at draw 1 according to trauma/PTSD status are presented in Table 1. Women in the no trauma group were slightly younger than those in the trauma/no PTSD group. Additionally, the mean number of years between blood draws was slightly longer for the no trauma group (13.5 years) compared to the trauma/no PTSD group (13.3 years). Compared to the other groups, women in the chronic PTSD group had healthier diets and were more likely to be non-drinkers, have comorbid depression, and use antidepressants. Women in the chronic PTSD group also had higher BMI than women in the no trauma group.

Median biomarker values at each draw, and median change in biomarker levels, according to trauma/PTSD status are shown in Table 2. Women with no trauma had the lowest CRP,

TNFRII, ICAM-1, and VCAM-1 levels at both assessments, whereas women with chronic PTSD had some of the highest biomarker levels. On average, biomarker levels increased over time in all groups.

Cross-Sectional Associations between Trauma, PTSD, and Biomarker Values

We found significant cross-sectional associations between trauma/PTSD status and average biomarker values across the two draws (Table 3). Full results from the linear mixed models for each biomarker are presented in Tables S1–S4. Compared to women without trauma, women with chronic PTSD had significantly higher average levels of CRP (b=0.27), TNFRII (b=0.07), and ICAM-1 (b=0.04) in multivariable-adjusted models (Table 3; see Table 4 for geometric mean concentrations and 95% CIs). Results with Winsorized biomarker values were highly similar (Table S5). Additionally, the trauma/no PTSD group had significantly higher TNFRII levels (b=0.05) compared to women without trauma (Table 3; see Table 4 for geometric mean concentrations and 95% CIs). No significant differences in average levels of VCAM-1 across groups were observed.

Longitudinal Associations between Trauma, PTSD, and Biomarker Values

Change in biomarker levels over time was relatively modest. On average, over 10 years there was a 9.0% increase in CRP, a 8.8% increase in TNFRII, a 3.0% increase in ICAM-1, and a 4.1% increase in VCAM-1. Overall, trauma/PTSD groups did not differ significantly in change in biomarker levels over time; evidence of significant trauma/PTSD × time interactions was observed only for VCAM-1 (Table 3). Women with chronic PTSD had a significantly greater increase in VCAM-1 over time compared to women without trauma (b=0.003) in multivariable-adjusted models. Findings with Winsorized biomarker values were similar (Table S5). To contextualize these findings in terms of raw biomarker values, we calculated the difference between the multivariable-adjusted geometric mean concentrations and 95% CIs for VCAM-1 at draw 1 and at draw 2 (mean follow-up 13.4 years). Expected value for the increase over the 13.4-year follow-up among women with chronic PTSD was 146.1ng/mL (138.1–154.3) versus 118.2ng/mL (112.4–124.2) among women without a history of trauma.

Associations between Trauma, PTSD, and Biomarker Values Adjusting for Behavioral Factors

We evaluated effects of adding behavior-related variables to models finding significant associations as reported above, and we found some support for the idea that these factors may lie on the pathway between PTSD and inflammation or impaired endothelial function. After adjusting for time-varying BMI, cigarette smoking, alcohol consumption, physical activity, and diet quality, we found associations of chronic PTSD (versus no trauma) with elevated CRP, TNFRII, and ICAM-1 were attenuated; only the associations between the chronic PTSD and trauma/no PTSD groups with elevated TNFRII approached statistical significance (Table 5). After adjusting for behavior-related variables, the trauma/PTSD status × time interactions for VCAM-1 were attenuated and no longer significant (Table 5).

Sensitivity Analyses

Overall, results were similar albeit somewhat attenuated when we covaried time-varying depression status and antidepressant use; most associations retained borderline statistical significance, whereas the associations of chronic PTSD and trauma/no PTSD with elevated TNFRII reached conventional statistical significance (Table S6). Antidepressant use was associated with higher CRP, TNFRII, and ICAM-1 levels and with greater increases in VCAM-1 levels over time, but no significant associations of depression status with any biomarkers were evident.

We also evaluated the hypothesis that longer duration of exposure to trauma/PTSD would be associated with higher biomarker levels. Women in the trauma/no PTSD and chronic PTSD groups had similar exposure duration, on average: 18.2 years between trauma and draw 1 for trauma/no PTSD versus 20.9 years for chronic PTSD, and 31.4 years between trauma and draw 2 for trauma/no PTSD versus 34.3 years for chronic PTSD. In trauma-exposed women, longer time between trauma and blood draw was associated with significantly higher average levels of all biomarkers (Table S7). Longer exposure to trauma/PTSD was also associated with higher average biomarker levels when separately considering women in the trauma/no PTSD and chronic PTSD groups (Table S7).

Discussion

Cross-sectional research has suggested that elevated inflammation and impaired endothelial function may help explain associations between PTSD and CVD risk(15,16,19–21). The current study extended this evidence by 1) investigating cross-sectional and longitudinal associations, and 2) comparing biomarker levels in women without trauma, with trauma but without PTSD, and with chronic PTSD. Compared to women with no trauma, women with chronic PTSD had higher average levels of CRP, TNFRII, and ICAM-1 over a 10–16-year period. Although we expected to find trauma/PTSD status would be associated with rate of change across all biomarkers, we found evidence of an association with only one biomarker; women with chronic PTSD showed steeper increases in VCAM-1 over follow-up compared to women without trauma.

Each biomarker represents a somewhat different inflammation-related process; thus, it is unclear if differential findings across biomarkers reflect true differences of effects or variation in measurement quality or are unique to this sample. For example, VCAM-1 is induced by pro-atherosclerotic conditions, and some evidence suggests that VCAM-1 may be especially predictive of CVD risk in high-risk individuals or those with pre-existing CVD(42). In contrast, ICAM-1 appears to be a general marker of inflammation in CVD-free individuals(42). Thus, it is possible that the significant longitudinal, but not cross-sectional, findings of chronic PTSD with VCAM-1 may reflect increasing risk of developing CVD over time, although we were not able to examine this question directly in our sample of CVD-free women. However, taken together, our findings are generally consistent and suggest that the chronic psychological consequences of trauma (i.e., PTSD)—rather than trauma exposure—may be particularly toxic as psychological symptoms were more strongly associated with markers of dysregulation in inflammatory and endothelial responses than trauma exposure alone. Our results also showed that longer time from trauma/PTSD onset to

blood draw was associated with greater elevations in biomarker levels. This finding is consistent with the Passos et al.(16) meta-analytic result that longer PTSD duration in years was positively associated with IL-1β levels. These results suggest that dysregulated inflammatory processes may be a marker of duration of trauma/PTSD exposure, but further research is needed to determine how much exposure time is required to initiate dysregulation and if such effects are reversible.

Results also showed that women with trauma but without PTSD had higher TNFRII levels compared to women without trauma, although not to as large a degree as women with chronic PTSD. This association was observed even after adjusting for depression and antidepressant use. Although we lacked a comprehensive assessment of other forms of psychopathology in these women, this finding is nonetheless consistent with literature suggesting that trauma exposure—even in the absence of measureable psychopathology—is associated with disruptions of biological stress responses that could lead to systemic inflammation(8,9). Furthermore, this trauma-related elevated inflammation could explain other findings in the literature suggesting that trauma exposure by itself is associated with some increased CVD risk(43,44). Nevertheless, it is of interest for future research to examine CVD risk biomarker profiles in women with trauma and other non-PTSD forms of psychopathology, such as depression.

Several physiological and behavioral mechanisms may explain the observed associations of chronic PTSD with elevated biomarkers of inflammation and impaired endothelial function. PTSD is characterized by dysregulation of the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary system that can lead to a cascade of harmful effects on immune and cardiovascular functioning(6,7). For example, heightened sympathetic activity is associated with elevated catecholamines, which have been linked to impaired endothelial function and increased cytokine production(7). Furthermore, a number of behaviors and conditions that increase risk for elevated inflammation and endothelial dysfunction(45,46), such as elevated BMI, physical inactivity, and cigarette smoking, have been observed more frequently in individuals with versus without PTSD(47,48). Indeed, in line with the hypothesis that BMI and poor health behaviors lie on the pathway from PTSD to inflammation and endothelial dysfunction, in the present study, associations were attenuated when accounting for these factors. These findings suggest that elevated BMI and unhealthy behaviors may be targets for intervention to offset heightened CVD risk among women with PTSD. Additional research is needed to examine if improving these factors among women with PTSD results in improvements in markers of inflammation and endothelial function.

Our study had several limitations. First, trauma/PTSD status, along with date of trauma exposure and PTSD onset, were based on retrospective self-report and could have been misclassified, which likely would have biased results toward the null. Second, we assessed *DSM-IV* PTSD because the study was conducted before the *DSM-5* revision. Additional research is needed to confirm whether similar findings are obtained using *DSM-5* diagnoses, although most *DSM-IV* PTSD criteria were retained in *DSM-5*. Third, although we examined two markers each of inflammation and endothelial function, the inflammatory cascade is complex and there are numerous markers that reflect endothelial health. Fourth, participants needed to survive until 2008 to provide trauma/PTSD information. Survivor bias

is a potential concern, although only 1.6% of the NHS II cohort was deceased by 2008. Fifth, generalizability of findings to more diverse samples is unclear, as the NHS II cohort is predominantly white professional women. Sixth, for the sake of parsimony, we did not include information on medical conditions like hypertension that might be on the pathway from PTSD to CVD risk biomarkers or occur simultaneously with these elevated biomarker values. However, these conditions are unlikely to be confounders because they are unlikely to cause PTSD(2). Seventh, we note that, overall, biomarker change over the 10–16-year period was modest. Indeed, we observed somewhat less change in biomarkers compared to other studies of change in inflammatory and endothelial function markers over ~7–10 years(49–51). Thus, it may have been more difficult to detect effects with respect to biomarker change.

Despite these limitations, the current study has several unique strengths. These include 1) considering biomarker change over time, 2) assessing PTSD with an interview, 3) comparing effects of no trauma with those of trauma/no PTSD and chronic PTSD, and 4) adjusting for a range of time-updated covariates. Inconsistency in covariates in studies of trauma, PTSD, and inflammatory biomarkers has been a major source of between-study heterogeneity in meta-analyses(15,16). That said, it is notable that our unadjusted findings were maintained after adjusting for key covariates, including age, menopausal status, and use of various medications. Consistent with many studies(16,52,53), we also found that PTSD remained associated with elevated biomarker levels when adjusting for depression status.

Conclusions

In a large community-based sample of middle-aged women without a history of CVD, chronic PTSD was characterized by a biomarker profile of heightened pro-inflammatory activity and impaired endothelial function compared to no trauma. Furthermore, preliminary evidence indicated that chronic PTSD, as compared with no trauma, was associated with greater increases in a marker of impaired endothelial function over a 10–16-year follow-up. Accumulating evidence links PTSD with CVD and accelerated aging(4); our study suggests that increased inflammation and impaired endothelial function may partly explain these associations. Going forward, it is critical to identify the duration of PTSD that leads to dysregulation of healthy biological processes and if improvement in PTSD symptoms may conversely reduce dysregulation. Our findings may suggest that more stringent surveillance of pre-disease risk factors and relevant risk markers among individuals with PTSD is valuable. Moreover, greater insight into the mechanisms by which PTSD may alter CVD risk will not only inform targeted prevention strategies, but also shed light on other disease endpoints for which individuals with PTSD may be at risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge the Channing Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital, and Harvard Medical School for managing the NHS II.

This study was supported by the National Institutes of Health grants R01MH078928, R01MH101269, UM1CA176726, K01HL130650, and T32MH017119, as well as the Yerby Postdoctoral Fellowship Program.

References

1. Levine AB, Levine LM, Levine TB. Posttraumatic stress disorder and cardiometabolic disease. Cardiology. 2014; 127:1–19. [PubMed: 24157651]
2. Koenen K, Sumner J, Gilsanz P, Glymour MM, Ratanatharathorn A, Rimm EB, et al. PTSD and cardiometabolic disease: improving causal inference to inform practice. Psychol Med. 2017; 47:209–225. [PubMed: 27697083]
3. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. Am J Hypertens. 2015; 28:1295–1302. [PubMed: 25911639]
4. Wolf EJ, Schnurr PP. Posttraumatic stress disorder-related cardiovascular disease and accelerated cellular aging. Psychiatr Ann. 2016; 46:527–532. [PubMed: 27990033]
5. Sumner JA, Kubzansky LD, Elkind MS, Roberts AL, Agnew-Blais J, Chen Q, et al. Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women. Circulation. 2015; 132:251–259. [PubMed: 26124186]
6. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. Nat Rev Neurosci. 2012; 13:769–787. [PubMed: 23047775]
7. Wentworth BA, Stein MB, Redwine LS, Xue Y, Taub PR, Clopton P, et al. Post-traumatic stress disorder: a fast track to premature cardiovascular disease? Cardiol Rev. 2013; 21:16–22. [PubMed: 22717656]
8. D'Andrea W, Sharma R, Zelechoski AD, Spinazzola J. Physical health problems after single trauma exposure: when stress takes root in the body. J Am Psychiatric Nurses Association. 2011; 17:378–392.
9. Yehuda R, Flory JD, Pratchett LC, Buxbaum J, Ising M, Holsboer F. Putative biological mechanisms for the association between early life adversity and the subsequent development of PTSD. Psychopharmacology. 2010; 212:405–417. [PubMed: 20706708]
10. Yeh ET, Willerson JT. Coming of age of C-reactive protein using inflammation markers in cardiology. Circulation. 2003; 107:370–371. [PubMed: 12551854]
11. Landmesser U, Hornig B, Drexler H. Endothelial function a critical determinant in atherosclerosis? Circulation. 2004; 109:II27–II33. [PubMed: 15173060]
12. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis. Annu Rev Immunol. 2009; 27:165–197. [PubMed: 19302038]
13. Black PH, Garbutt LD. Stress, inflammation, and cardiovascular disease. J Psychosom Res. 2002; 52:1–23. [PubMed: 11801260]
14. Blake GJ, Ridker PM. Inflammatory bio-markers and cardiovascular risk prediction. J Intern Med. 2002; 252:283–294. [PubMed: 12366601]
15. Tursich M, Neufeld R, Frewen P, Harricharan S, Kibler JL, Rhind SG, et al. Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis. Transl Psychiatry. 2014; 4:e413. [PubMed: 25050993]
16. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015; 2:1002–1012. [PubMed: 26544749]
17. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010; 67:446–457. [PubMed: 20015486]
18. Liu Y, Ho RC-M, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012; 139:230–239. [PubMed: 21872339]
19. Plantinga L, Bremner JD, Miller AH, Jones DP, Veledar E, Goldberg J, et al. Association between posttraumatic stress disorder and inflammation: a twin study. Brain Behav Immun. 2013; 30:125–132. [PubMed: 23379997]

20. von Känel R, Abbas CC, Begré S, Saner H, Gander ML, Schmid JP. Posttraumatic stress disorder and soluble cellular adhesion molecules at rest and in response to a trauma-specific interview in patients after myocardial infarction. Psychiatry Res. 2010; 179:312–317. [PubMed: 20488551]
21. Farr O, Ko BJ, Joung K, Zaichenko L, Usher N, Tsoukas M, et al. Posttraumatic stress disorder, alone or additively with early life adversity, is associated with obesity and cardiometabolic risk. Nutr Metab Cardiovasc Dis. 2015; 25:479–488. [PubMed: 25770759]
22. von Känel R, Hepp U, Traber R, Kraemer B, Mica L, Keel M, et al. Measures of endothelial dysfunction in plasma of patients with posttraumatic stress disorder. Psychiatry Res. 2008; 158:363–373. [PubMed: 18252265]
23. Smith AK, Conneely KN, Kilaru V, Mercer KB, Weiss TE, Bradley B, et al. Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet. 2011; 156:700–708.
24. Jergović M, Bendelja K, Mlakar AS, Vojvoda V, Aberle N, Jovanovic T, et al. Circulating levels of hormones, lipids, and immune mediators in post-traumatic stress disorder–a 3-month follow-up study. Front Psychiatry. 2015; 6:49. [PubMed: 25926799]
25. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000; 342:836–843. [PubMed: 10733371]
26. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med. 2004; 351:2599–2610. [PubMed: 15602020]
27. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA. 2004; 291:1978–1986. [PubMed: 15113816]
28. Huang T, Tobias DK, Hruby A, Rifai N, Tworoger SS, Hu FB. An increase in dietary quality is associated with favorable plasma biomarkers of the brain-adipose axis in apparently healthy US women. J Nutr. 2016; 146:1101–1108. [PubMed: 27075907]
29. Koenen KC, De Vivo I, Rich-Edwards J, Smoller JW, Wright RJ, Purcell SM. Protocol for investigating genetic determinants of posttraumatic stress disorder in women from the Nurses' Health Study II. BMC Psychiatry. 2009; 9:29. [PubMed: 19480706]
30. Roberts AL, Dohrenwend BP, Aiello AE, Wright RJ, Maercker A, Galea S, et al. The stressor criterion for posttraumatic stress disorder: Does it matter? J Clin Psychiatry. 2012; 73:264–270.
31. Sumner JA, Kubzansky LD, Kabrhel C, Roberts AL, Chen Q, Winning A, et al. Associations of trauma exposure and posttraumatic stress symptoms with venous thromboembolism over 22 years in women. J Am Heart Assoc. 2016; 5:e003197. [PubMed: 27172912]
32. Sumner J, Kubzansky L, Roberts A, Gilsanz P, Chen Q, Winning A, et al. Post-traumatic stress disorder symptoms and risk of hypertension over 22 years in a large cohort of younger and middle-aged women. Psychol Med. 2016; 46:3105–3116. [PubMed: 27534802]
33. Morgan CA III, Hazlett G, Wang S, Richardson EG Jr, Schnurr P, Southwick SM. Symptoms of dissociation in humans experiencing acute, uncontrollable stress: a prospective investigation. Am J Psychiatry. 2001; 158:1239–1247. [PubMed: 11481157]
34. Breslau N, Peterson EL, Kessler RC, Schultz LR. Short screening scale for DSM-IV posttraumatic stress disorder. Am J Psychiatry. 1999; 156:908–911. [PubMed: 10360131]
35. Rich-Edwards JW, Mason S, Rexrode K, Spiegelman D, Hibert E, Kawachi I, et al. Physical and sexual abuse in childhood as predictors of early onset cardiovascular events in women. Circulation. 2012; 126:920–927. [PubMed: 22787111]
36. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology. 1990; 1:466–473. [PubMed: 2090285]
37. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr. 2012; 142:1009–1018. [PubMed: 22513989]
38. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993; 31:247–263. [PubMed: 8450681]

39. Silveira E, Taft C, Sundh V, Waern M, Palsson S, Steen B. Performance of the SF-36 health survey in screening for depressive and anxiety disorders in an elderly female Swedish population. Qual Life Res. 2005; 14:1263–1274. [PubMed: 16047502]
40. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16:606–613. [PubMed: 11556941]
41. Bell, BA., Ene, M., Schoeneberger, J. A multilevel model primer using SAS PROC MIXED. Paper presented at: SAS Global Forum; San Francisco, CA. 2013.
42. Blankenberg S, Barbaux S, Tiret L. Adhesion molecules and atherosclerosis. Atherosclerosis. 2003; 170:191–203. [PubMed: 14612198]
43. Husarewycz MN, El-Gabalawy R, Logsetty S, Sareen J. The association between number and type of traumatic life experiences and physical conditions in a nationally representative sample. Gen Hosp Psychiatry. 2014; 36:26–32. [PubMed: 24183489]
44. Scott KM, Koenen KC, Aguilar-Gaxiola S, Alonso J, Angermeyer MC, Benjet C, et al. Associations between lifetime traumatic events and subsequent chronic physical conditions: a cross-national, cross-sectional study. PloS One. 2013; 8:e80573. [PubMed: 24348911]
45. Gordon JL, Lavoie KL, Arsenault A, Ditto B, Bacon SL. Health behaviors and endothelial function. J Behav Med. 2008; 31:5–21. [PubMed: 17906923]
46. McDade TW, Hawkley LC, Cacioppo JT. Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago, Health, Aging, and Social Relations Study. Psychosom Med. 2006; 68:376–381. [PubMed: 16738067]
47. Kubzansky LD, Bordelois P, Jun HJ, Roberts AL, Cerda M, Bluestone N, et al. The weight of traumatic stress: a prospective study of posttraumatic stress disorder symptoms and weight status in women. JAMA Psychiatry. 2014; 71:44–51. [PubMed: 24258147]
48. Zen AL, Whooley MA, Zhao S, Cohen BE. Post-traumatic stress disorder is associated with poor health behaviors: findings from the heart and soul study. Health Psychol. 2012; 31:194–201. [PubMed: 22023435]
49. Fontes JD, Yamamoto JF, Larson MG, Wang N, Dallmeier D, Rienstra M, et al. Clinical correlates of change in inflammatory biomarkers: the Framingham Heart Study. Atherosclerosis. 2013; 228:217–223. [PubMed: 23489346]
50. Hamer M, Sabia S, Batty GD, Shipley MJ, Tabák AG, Singh-Manoux A, et al. Physical activity and inflammatory markers over 10 years follow-up in men and women from the Whitehall II Cohort Study. Circulation. 2012; 126:928–933. [PubMed: 22891048]
51. Nash SD, Cruickshanks KJ, Klein R, Klein BE, Nieto FJ, Chappell R, et al. Long-term variability of inflammatory markers and associated factors in a population-based cohort. J Am Geriatr Soc. 2013; 61:1269–1276. [PubMed: 23889670]
52. Heath NM, Chesney SA, Gerhart JI, Goldsmith RE, Luborsky JL, Stevens NR, et al. Interpersonal violence, PTSD, and inflammation: potential psychogenic pathways to higher C-reactive protein levels. Cytokine. 2013; 63:172–178. [PubMed: 23701836]
53. Canetti D, Russ E, Luborsky J, Gerhart JI, Hobfoll SE. Inflamed by the flames? The impact of terrorism and war on immunity. J Trauma Stress. 2014; 27:345–352. [PubMed: 24948537]

Table 1

Participant characteristics at draw 1 according to trauma/PTSD status (*N*=524).

	No trauma (*n*=175)	Trauma/no PTSD (*n*=175)	Chronic PTSD (*n*=174)	
	% (n) or Mean (SD)	% (n) or Mean (SD)	% (n) or Mean (SD)	*P*-value[a]
Mean age, years	42.9 (4.8)	44.5 (4.8)	44.0 (4.6)	.005
Mean time between blood draws, years	13.5 (0.9)	13.3 (1.1)	13.4 (0.9)	.04
White race, %	96.6 (169)	97.1 (170)	96.6 (168)	.62
BMI, kg/m^2	25.1 (5.5)	25.4 (4.9)	26.6 (6.2)	.03
Current smoking in last month, %	5.7 (10)	4.0 (7)	9.2 (16)	.11
Alcoholic drinks in last month, %				.04
0	30.9 (54)	34.5 (60)	47.7 (82)	
1–3/month	26.3 (46)	31.6 (55)	26.2 (45)	
1/week	12.0 (21)	8.1 (14)	5.2 (9)	
2–4/week	15.4 (27)	12.6 (22)	10.5 (18)	
5+/week	15.4 (27)	13.2 (23)	10.5 (18)	
Physical activity frequency, %				.07
<1/week	31.0 (54)	40.8 (71)	34.3 (59)	
1/week	20.1 (35)	17.2 (30)	27.9 (48)	
2–3/week	36.8 (64)	27.6 (48)	26.2 (45)	
4+/week	12.1 (21)	14.4 (25)	11.6 (20)	
AHEI scoreb	50.3 (10.2)	50.5 (9.5)	52.9 (10.5)	.03
Pre-menopausal status, %	78.3 (137)	72.6 (127)	69.0 (120)	.12
Hormone therapy use in past month, %	16.6 (29)	22.3 (39)	17.2 (30)	.35
Anti-inflammatory use, %	55.4 (97)	56.6 (99)	65.5 (114)	.11
Anti-hypertensive use, %	6.3 (11)	12.6 (22)	12.6 (22)	.08
Cholesterol-lowering medication use, %	1.7 (3)	4.0 (7)	4.0 (7)	.38
Depression, c %	8.7 (15)	2.9 (5)	25.4 (43)	<.0001
Antidepressant use, %	5.7 (10)	8.6 (15)	35.6 (62)	<.0001

Note. PTSD=posttraumatic stress disorder. BMI=body mass index. AHEI=Alternate Healthy Eating Index.

[a] *P*-values correspond to omnibus tests.

[b] Higher AHEI scores indicate a healthier diet.

[c] Depression defined as a score less than 53 on the Short Form-36 Mental Health scale.

Biol Psychiatry. Author manuscript; available in PMC 2018 December 15.

Table 2

Inflammatory marker and endothelial cell adhesion molecule levels according to trauma/PTSD status (*N*=524).

	Draw 1		Draw 2				
	Median (Interquartile Range)	***n***	**Median (Interquartile Range)**	***n***	**Median Change Score (Interquartile Range)**	***n***	**ICC[a]**
CRP, mg/L							0.68
No trauma	0.90 (0.37, 2.37)	175	1.00 (0.42, 2.12)	173	0.08 (−0.29, 0.52)	173	
Trauma/no PTSD	1.08 (0.44, 3.60)	175	1.30 (0.61, 3.16)	173	0.11 (−0.59, 0.81)	173	
Chronic PTSD	1.27 (0.55, 3.46)	173	1.58 (0.68, 3.25)	174	0.16 (−0.63, 1.16)	174	
TNFRII, pg/mL							0.58
No trauma	2102.3 (1827.5, 2520.3)	175	2324.5 (2020.8, 2740.0)	173	224.3 (−21.0, 456.8)	173	
Trauma/no PTSD	2299.4 (1985.3, 2599.4)	175	2556.0 (2167.6, 3060.4)	174	266.5 (−16.4, 549.1)	174	
Chronic PTSD	2258.0 (1949.3, 2639.5)	174	2552.9 (2174.8, 3008.9)	173	306.0 (−63.4, 600.9)	173	
ICAM-1, ng/mL							0.67
No trauma	228.4 (206.8, 258.6)	175	241.1 (215.7, 274.5)	173	9.6 (−7.1, 27.9)	173	
Trauma/no PTSD	232.7 (208.0, 266.8)	175	247.4 (216.1, 274.0)	174	13.2 (−11.4, 35.0)	174	
Chronic PTSD	241.1 (211.5, 274.0)	174	249.3 (221.9, 294.7)	174	10.7 (−17.3, 33.8)	174	
VCAM-1, ng/mL							0.66
No trauma	633.5 (551.6, 743.6)	175	659.4 (568.8, 748.9)	173	12.6 (−55.7, 66.0)	173	
Trauma/no PTSD	642.6 (551.8, 731.8)	175	661.6 (593.3, 778.8)	174	34.4 (−37.2, 118.4)	174	
Chronic PTSD	640.9 (546.3, 753.1)	174	681.0 (578.1, 788.8)	174	52.7 (−31.6, 104.8)	174	

Note. PTSD=posttraumatic stress disorder. ICC=intraclass correlation coefficient. CRP=C-reactive protein. TNFRII=tumor necrosis factor-alpha receptor-II. ICAM-1=intercellular adhesion molecule-1. VCAM-1=vascular cell adhesion molecule-1.

[a]The ICC is the ratio of between-person variance to total variance, and provides information on how much of the overall variation in biomarker levels is explained by individual differences between participants.

Table 3

Trauma/PTSD status regression coefficient estimates and standard errors from the linear mixed models predicting inflammatory markers and endothelial cell adhesion molecules (*N*=524).

	CRP		TNFRII		ICAM-1		VCAM-1	
(a) Cross-sectional Model								
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Trauma/PTSD Status								
No trauma	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
Trauma/no PTSD	0.16 (0.11)	0.17 (0.11)	0.05 (0.02)*	0.05 (0.02)*	0.00 (0.02)	0.01 (0.02)	0.01 (0.02)	0.01 (0.02)
Chronic PTSD	0.29 (0.11)*	0.27 (0.11)*	0.07 (0.02)**	0.07 (0.02)**	0.05 (0.02)*	0.04 (0.02)*	0.01 (0.02)	0.01 (0.02)
(b) Longitudinal Model								
	Model 1[a]	Model 2[c]	Model 1[a]	Model 2[c]	Model 1[a]	Model 2[c]	Model 1[a]	Model 2[c]
Trauma/PTSD Status								
No trauma	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
Trauma/no PTSD	0.14 (0.13)	0.13 (0.12)	0.05 (0.03)+	0.05 (0.03)*	0.00 (0.02)	0.00 (0.02)	0.00 (0.02)	0.00 (0.02)
Chronic PTSD	0.25 (0.12)*	0.22 (0.12)+	0.06 (0.03)**	0.07 (0.03)**	0.06 (0.02)**	0.06 (0.02)*	−0.01 (0.02)	0.00 (0.02)
Time[d]	0.006 (0.005)	0.005 (0.014)	0.008 (0.001)***	0.008 (0.002)**	0.003 (0.001)**	0.002 (0.002)	0.001 (0.001)	0.003 (0.003)
Interaction Terms								
No trauma x Time	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
Trauma/no PTSD x Time	0.003 (0.008)	0.008 (0.007)	0.002 (0.002)	0.001 (0.002)	0.001 (0.001)	0.000 (0.001)	0.003 (0.001)+	0.002 (0.001)
Chronic PTSD x Time	0.006 (0.008)	0.009 (0.008)	0.002 (0.002)	0.002 (0.002)	−0.002 (0.001)	−0.002 (0.001)	0.004 (0.001)*	0.003 (0.001)*

Notes. PTSD=posttraumatic stress disorder. CRP=C-reactive protein. TNFRII=tumor necrosis factor-alpha receptor-II. ICAM-1=intercellular adhesion molecule-1. VCAM-1=vascular cell adhesion molecule-1. Biomarkers were log-transformed.

[a]Adjusted for age at draw 1 (grand-mean centered) and time in years since draw 1.

[b]Adjusted for Model 1 covariates plus race and time-updated anti-hypertensive medication use, anti-inflammatory medication use, cholesterol-lowering medication use, menopausal status, and hormone therapy use.

[c]Adjusted for Model 1 covariates plus race and time-updated anti-hypertensive medication use, anti-inflammatory medication use, cholesterol-lowering medication use, menopausal status, and hormone therapy use and significant interactions of these covariates × time.

[d] Time in years since draw 1.

[+] $p<.10$,

[*] $p<.05$,

[**] $p<.01$

Table 4

Least-squares geometric means and 95% confidence intervals of the inflammatory markers and endothelial cell adhesion molecules in the raw scale for each trauma/PTSD group, calculated based on the cross-sectional trauma/PTSD main effect linear mixed models (*N*=524).

	CRP, mg/L		TNFRII, pg/mL		ICAM-1, ng/mL		VCAM-1, ng/mL	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Trauma/PTSD Status								
No trauma	1.06 (0.91, 1.24)	1.16 (0.80, 1.68)	2295.0 (2220.7, 2372.0)	2308.4 (2133.0, 2498.1)	238.9 (232.2, 245.9)	244.0 (227.9, 261.2)	651.8 (631.6, 672.5)	615.0 (570.7, 662.6)
Trauma/no PTSD	1.25 (1.07, 1.46)	1.37 (0.94, 2.00)	2422.4 (2344.0, 2503.4)	2436.0 (2250.0, 2637.3)	240.1 (233.3, 247.1)	245.4 (229.1, 262.7)	661.1 (640.7, 682.1)	624.2 (579.1, 672.8)
Chronic PTSD	1.42 (1.22, 1.67)	1.52 (1.05, 2.20)	2472.0 (2392.0, 2554.7)	2488.2 (2301.0, 2690.8)	250.6 (243.5, 257.8)	254.8 (238.1, 272.6)	660.9 (640.6, 681.9)	626.1 (581.5, 674.2)

Notes. PTSD=posttraumatic stress disorder. CRP=C-reactive protein. TNFRII=tumor necrosis factor-alpha receptor-II. ICAM-1=intercellular adhesion molecule-1. VCAM-1=vascular cell adhesion molecule-1.

[a]Adjusted for age at draw 1 (grand-mean centered) and time in years since draw 1.

[b]Adjusted for Model 1 covariates plus race and time-updated anti-hypertensive medication use, anti-inflammatory medication use, cholesterol-lowering medication use, menopausal status, and hormone therapy use.

Table 5

Trauma/PTSD status regression coefficient estimates and standard errors from linear mixed models predicting inflammatory markers and endothelial cell adhesion molecules after including BMI and behavioral factors (n=521).

	CRP	TNFRII	ICAM-1	VCAM-1
Fixed Effects				
Intercept	0.06 (0.09)	7.75 (0.02) ***	5.46 (0.02) ***	6.49 (0.02) ***
Time	0.009 (0.004) **	0.009 (0.001) ***	0.004 (0.001) ***	0.005 (0.001) **
Age at draw 1	0.039 (0.008) ***	0.010 (0.002) ***	0.007 (0.002) ***	0.001 (0.002)
Trauma/PTSD				
No trauma (ref)	---	---	---	---
Trauma/no PTSD	0.12 (0.09)	0.04 (0.02) +	-0.01 (0.02)	0.00 (0.02)
Chronic PTSD	0.14 (0.09)	0.04 (0.02) +	0.03 (0.02)	0.01 (0.02)
Trauma/PTSD x Time				
No trauma x Time (ref)	---	---	---	---
Trauma/no PTSD x Time	---	---	---	0.002 (0.002)
Chronic PTSD x Time	---	---	---	0.001 (0.002)
Cigarette smoking				
0 (ref)	---	---	---	---
1–4/day	−0.48 (0.24) *	−0.06 (0.06)	0.00 (0.05)	−0.06 (0.05)
5+/day	0.21 (0.16)	0.05 (0.04)	0.25 (0.03) ***	−0.07 (0.04) *
Alcoholic drink consumption				
0 (ref)	---	---	---	---
1–3/month	0.00 (0.07)	−0.05 (0.02) **	0.00 (0.01)	0.01 (0.02)
1/week	−0.01 (0.10)	−0.06 (0.02) **	−0.01 (0.02)	−0.01 (0.03)
2–4/week	−0.03 (0.09)	−0.07 (0.02) **	−0.03 (0.02)	−0.03 (0.03)
5+/week	0.02 (0.10)	−0.12 (0.02) ***	−0.03 (0.02)	−0.07 (0.03) *
Physical activity				
<1/week (ref)	---	---	---	---
1/week	0.09 (0.09)	−0.02 (0.02)	0.02 (0.02)	−0.03 (0.02)
2–3/week	−0.03 (0.07)	−0.02 (0.02)	0.00 (0.01)	−0.01 (0.02)
4+/week	0.00 (0.08)	−0.02 (0.02)	0.00 (0.02)	−0.03 (0.02)
BMI	0.120 (0.006) ***	0.012 (0.001) ***	0.008 (0.001) ***	−0.010 (0.002) ***
AHEI score	−0.006 (0.004)	0.000 (0.001)	−0.001 (0.001)	−0.001 (0.001)
Alcoholic drink consumption x Time				
0 x Time (ref)	---	---	---	---
1–3/month x Time	---	---	---	−0.005 (0.002) *
1/week x Time	---	---	---	−0.001 (0.003)
2–4/week x Time	---	---	---	−0.001 (0.002)
5+/week x Time	---	---	---	−0.006 (0.002) **

	CRP	TNFRII	ICAM-1	VCAM-1
BMI x Time	---	---	---	0.001 (0.0001)***
Error Variance				
Level-1	0.395 (0.026)***	0.019 (0.002)***	0.013 (0.001)***	0.012 (0.002)***
Intercept	0.499 (0.047)***	0.028 (0.003)***	0.024 (0.002)***	0.036 (0.003)***
Time	---	0.00003 (0.00002)+	---	0.00004 (0.00002)*

Notes. PTSD=posttraumatic stress disorder. BMI=body mass index. CRP=C-reactive protein. TNFRII=tumor necrosis factor-alpha receptor-II. ICAM-1=intercellular adhesion molecule-1. VCAM-1=vascular cell adhesion molecule-1. AHEI=Alternate Healthy Eating Index. Biomarkers were log-transformed. Time=years since draw 1. Age at draw 1, BMI, and AHEI score were grand-mean centered. Behavioral factors were time-updated to reflect values at draws 1 and 2.

+ $p<.10$,

* $p<.05$,

** $p<.01$,

*** $p<.0001$